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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,302	05/31/2005	Pasqua Anna Oreste	GRT/3687-101	7086

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EXAMINER	
BLAND, LAYLA D	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
06/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,302	ORESTE ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-134* is/are pending in the application.

4a) Of the above claim(s) *71-89,110-131 and 134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-109 and 132-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is a response to Applicant's amendment submitted April 3, 2009, wherein claims 90, 94, 106, and 107 are amended.

Claims 71-89, 110-131 and 134 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 16, 2008.

Claims 71-134 are pending. Claims 71-89, 110-131 and 134 are withdrawn from consideration. Claims 90-109, 132, and 133 are examined on the merits herein.

In view of Applicant's amendment submitted April 3, 2009, the objection to claim 4 for informalities is withdrawn.

In view of Applicant's remarks submitted April 3, 2009, the rejection of claim 90 under 35 USC 112, second paragraph, for indefiniteness with respect to "sulfation degree of at least 4" is withdrawn. Applicant clarified that the maximum degree of sulfation is 5.

In view of Applicant's amendment submitted April 3, 2009, the rejection of claim 90 under 35 USC 112, second paragraph, for indefiniteness with respect to "basically inactive for coagulation" is withdrawn because the limitation was removed.

In view of Applicant's amendment submitted April 3, 2009, the rejection of claim 94 under 35 USC 112, second paragraph, for indefiniteness with respect to "remaining uronic units" is withdrawn because the limitation was removed.

In view of Applicant's amendment submitted April 3, 2009, the rejection of claim 106 under 35 USC 112, second paragraph, for indefiniteness with respect to inconsistencies in iduronic acid content is withdrawn. The dependency of claim 106 was changed.

The rejection of claims 90, 91, 93, and 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leali is withdrawn because the claims require an iduronic acid content of 20-60%, which is not taught by Leali. Applicant's argument that the Examiner totally and deliberately misreads the definition of epiK5 in the specification is noted. However, the definition given in the specification, "epiK5" is meant the K5 and its derivatives in which 20-60% of the glucuronic units is C-5 epimerized to iduronic units, can be reasonably read in two ways. One reading is: "epiK5" is the K5 and derivatives of the K5 in which the glucuronic units are epimerized; the other is: "epiK5" is K5 in which the glucuronic units are epimerized and derivatives of K5 in which the glucuronic units are epimerized. The point is moot because claim 90 requires an iduronic acid content of 20-60%, but the Examiner would like to draw Applicant's attention to the matter for the sake of future amendments.

The rejection of claims 90-109 and 132-133 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 7,268,122 in view of Casu is withdrawn. Applicant's argument is persuasive.

The rejection of claims 90-109 and 132-133 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27

of U.S. Patent No. 6,992,183 in view of Casu is withdrawn. Applicant's argument is persuasive.

The following rejections of record are maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 103 and 107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 103 is drawn to a LMW-epiK5-N,O-oversulfate having a mean molecular weight from approximately 2,000 to approximately 16,000. The specification, page 7, states that LMW means "from approximately 1,500 to approximately 12,000." The limitations of claim 103 fall outside the definition of LMW given in the specification. Thus, the meaning of "LMW" is unclear.

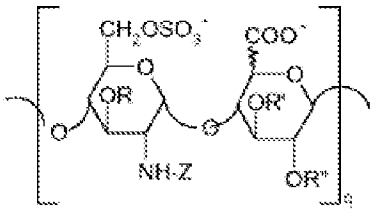
Claim 107 ultimately depends from claim 98 and recites formula III'b. Formula III'b contains moieties which fall outside of the definition in claim 98.

Response to Arguments

Applicant argues that the abbreviation LMW is not limited to 1500-12,000 daltons as alleged by the Examiner, and that 1500-12,000 is only an example. The specification, page 7, states that "LMW" products are "consisting of or derived from K5-N-sulfates having a mean molecular weight from approximately 1,500 to approximately

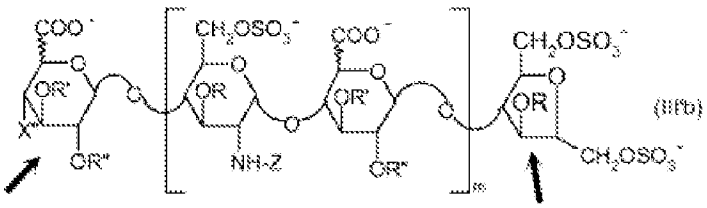
12,000." This appears to be a limiting definition. However, if Applicant intends this to be only exemplary, then there is no limit on molecular weight for LMW products. Applicant also argues that the range recited in claim 103 is indicative of molecular weight distribution, as opposed to mean molecular weight recited in the specification. This argument is not persuasive because claim 103 clearly states "mean molecular weight." Thus, “LMW” is still unclear and the rejection is maintained.

Applicant states that it is unclear why the Examiner objects to claim 107. Claim 98, from which claim 107 ultimately depends, is drawn to a product wherein 90% of the chains have the following formula:



(IIf')

Thus, claim 98 is drawn to a product wherein 90% of the chains consist of a repeating unit of the above disaccharide. However, claim 107 is drawn to a product wherein the preponderant species has the following formula:



(IIfb)

Applicant's attention is drawn to the saccharide units indicated by arrows. If at least 90% of the chains are of the formula in claim 98, a repeating disaccharide unit, it is

unclear how the preponderant species can contain moieties other than those found in 90% of the chains.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 90-109 and 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casu. (WO 98/42754, October 1, 1998, of record) in view of Leali (The Journal of Biological Chemistry, Vol. 276, No. 41, Issue of October 12, pp. 37900-37908, 2001, of record).

Casu teaches products prepared from either K5 polysaccharide or epimerized K5 polysacharide [page 10, lines 1-8]. The products have a sulfate/carboxyls molar ratio from 2.0 to 3.5 and molecular weight of 1,500-8,000 or 8,000 to 18,000, or 8,000 to 25,000 [claims 1-5]. The epimerized products are 30:70 or 60:30 iduronic acid to glucuronic acid [page 10, lines 5-7]. The products are prepared using sodium acetate [page 11, part d], which would be expected to give the sodium salt. Casu also teaches that low molecular weight heparins have lower anticoagulant activity and better bioavailability compared to traditional heparins [page 2, lines 10-21]. Supersulfated glycosaminoglycans can be prepared by methods known in the art [page 4, lines 15-18].

Casu does not teach products having a sulfation degree of greater than 3.5.

Leali teaches highly N,O-sulfated K5 polysaccharide derivatives [see abstract and Figure 1]. In one example, the degree of sulfation was 3.84 and the molecular weight was 15,000 [Table I]. The degree of sulfation modulates the biological activity of sulfated K5 derivatives. N-sulfation is a requirement for angiostatic activity of K5 derivatives that must also be sulfated in O positions [page 37907, first column, last paragraph]. The highly N,O-sulfated K5 derivative exerts a potent FGF2 antagonist and angiostatic activity and has low anticoagulant activity, which makes highly sulfated K5 derivatives attractive targets for design of novel therapeutic compounds [page 37907, last paragraph].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare highly sulfated products from epimerized or non-epimerized K5, as taught by Casu, with a high degree of sulfation in order to obtain a product with activity as taught by Leali. Casu teaches that either K5 or epimerized K5 can be used to prepare biologically active supersulfated glycosaminoglycans which are similar to heparin. Since Leali teaches the desirability of a highly sulfated K5 product, the skilled artisan could envision using low molecular weight products and highly sulfated products, and could reasonably expect success in preparing such products because Casu teaches that methods of supersulfation are known in the art.

Claims 90-109 and 132-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casu in view of Leali as applied to claims 90-109 and 132 above, and further in view of Oreste (US 2002/0062019, May 23, 2002, of record).

Casu and Leali teach as set forth above. Casu and Leali do not teach a cosmetic composition.

Oreste teaches glycosaminoglycans derived from epimerized K5 polysaccharides which have been subjected to O-oversulfation and N-sulfation [see abstract]. An additional N-sulfation step is required because some N-sulfate groups are lost during O-oversulfation [0120]. In one example, the molecular weight is 7,000 and about 55% of the uronic acid units are those of iduronic acid [claim 44]. Sodium or calcium salts are taught [claim 46]. Topical compositions comprising carriers such as gels, creams, or lotions are taught [0185]. These could be considered cosmetic compositions.

It would have been obvious to one of ordinary skill in the art to prepare a cosmetic composition comprising the derivatives as discussed above. Leali, Casu, and Oreste all teach glycosaminoglycans prepared from K5 polysaccharide, which are O-sulfated and N-sulfated. Oreste teaches that these can be used in a topical composition with lotions or creams, so it would have been obvious to prepare the same type of composition using the derivatives as discussed above.

Response to Arguments

Applicant argues that the prior art does not teach methods to achieve sulfation degrees of at least 4, that the office action provides no evidence of a reasonable expectation of success, and that accomplishment of that effect is a result of "wishfulness." As set forth above, Casu teaches that supersulfation methods are known in the art. Thus, the skilled artisan would have a reasonable expectation of success in preparing highly sulfated products, because processes for preparing them are known.

"Obviousness does not require absolute predictability of success." *Id.* at 903, 7"USPQ2d at 1681.1. Applicant's attention is drawn to Guo (US 6,388,060, May 14, 2002), which teaches methods for achieving high levels of sulfation in uronic acid-containing polysaccharides, and van Boeckel (US 5,071,969, December 10, 1991), which teaches that reaction time and quantity of sulfation reagent used determine the degree of sulfation [column 2, lines 44-52].

Applicant argues that the difference in degrees of sulfation between Leali's product (3.8) and Example 4 (4.4) is a large difference. This argument is not persuasive because the claims are not drawn to products which have a sulfation degree of at least 4.4; the claims require a sulfation degree of at least 4. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that the claimed products have unexpected activity: antiangiogenic and antiviral, and substantially free of coagulation activity. It is noted that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., In re Huang, 100 F.3d 135,139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). The burden is shifted to Applicant to show factually supported objective evidence to rebut the prima facie case of obviousness over the prior art.

Applicant argues that Oreste teaches away from products having a sulfation degree of at least 4, and that Oreste's products are used for regulation of coagulation and thrombosis. Claim 133 requires a composition which includes a "cosmetic

excipient." Oreste's compositions, comprising sulfated epiK5 polysaccharides, are described as topical compositions which comprise pharmaceutically acceptable carriers or diluents known in the art for preparation of gels, cream, ointments, lotions, or solutions to be sprayed. Carriers and diluents used for the preparation of gels, creams, ointments, lotions, etc. are also suitable for cosmetic compositions. Although Oreste's products are not as highly sulfated as Casu's products, they are similar products used for a similar purpose and thus Oreste does not teach away.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Monday - Friday, 7:00 - 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Layla Bland/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
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